Targeting Viral Ion Channels: An Efficient Strategy to Develop Antivirals

Hiya Lahiri* and Isaiah T. Arkin

Department of Biomedical Engineering, City University of Hong Kong, Hong Kong SAR, China
E-mail: hlahiri@cityu.edu.hk

Many viruses are found to contain small hydrophobic proteins that can form ion channels, collectively termed viroporins.[1] Such proteins can serve as potential targets for drug molecules to develop new antivirals. Aminoadamantanes are a well-known class of drugs that can block the well-characterized M2 ion channel of the influenza virus. However, the need for an M2 channel blocker increased due to its rapid mutation, which makes the channel resistant to adamantanes. To find new blockers, we screened a diverse compound library using three bacteria-based unique screening assays. The hit compounds were then subjected to in vitro and in vivo studies. Interestingly, we found a combination of two compounds, theobromine and arainosine, shows excellent synergistic effects at nanomolar concentrations and outperforms commercially available anti-flu drugs. Moreover, when we did resistance profiling by utilizing bacterial genetic selection, we found that this drug duo has a lower chance to evoke drug-resistance, and the pattern is strikingly different from amionodamantanes.[2] We employed the above-stated unique approach to find an antiviral against the Chikungunya virus. We found several blockers by targeting the 6K ion channel of CHIKV; some of them successfully blocked 6K from another alphavirus, Eastern equine encephalitis virus (EEEV), while others were not. To conclude, we focused on structural specificity by employing structure-prediction tools and molecular dynamics simulations to elucidate the probable structures of the corresponding ion channels.[3] We also characterized several potential viroporins from flaviviruses, such as dengue virus type 1, West Nile virus, and Zika. Several drugs exhibited potential blocking activity when assessed using bacteria-based assays[4] followed by an in vitro assay, and were found to be highly active against live viruses.

References

1. *FEBS Lett*. **2003**, 552, 28–34.
2. *Proc Natl Acad Sci U S A* **2025,** *122* (31), e2502240122.
3. *Molecules* **2025**, 30, 3942.
4. *Viruses* **2022**, 14, 1750.